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Synthesis of Hydroxybenzyl Compounds

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A one-step synthesis of 2-, and 4-hydroxybenzyl compounds from the corresponding acetoxybenzyl acetates is described. This convenient procedure gives hydroxybenzyl methyl ethers, N,N-diethyl-hydroxybenzyl amines, N-phenyl-hydroxybenzyl amines, hydroxybenzyl azides, hydroxybenzyl cyanides *etc.* in fair yields.

INTRODUCTION

Concerning the synthesis of hydroxybenzyl compounds, it is thought that the corresponding halides serve as starting materials. However, free hydroxybenzyl halides have never been made because of their instability.^{1,2)} Therefore, acetoxybenzyl halides prepared by troublesome methods,¹⁻⁵⁾ are commonly used. We have found that 2-, and 4-acetoxybenzyl acetate that are easily prepared by treatment of hydroxybenzyl alcohols with acetic anhydride are suitable for the purpose except for the 3-isomer. In this study, the synthesis of hydroxybenzyl compounds from their acetates was carried out but no attempt was made to determine the conditions for the maximum yield of each reaction.

RESULTS AND DISCUSSION

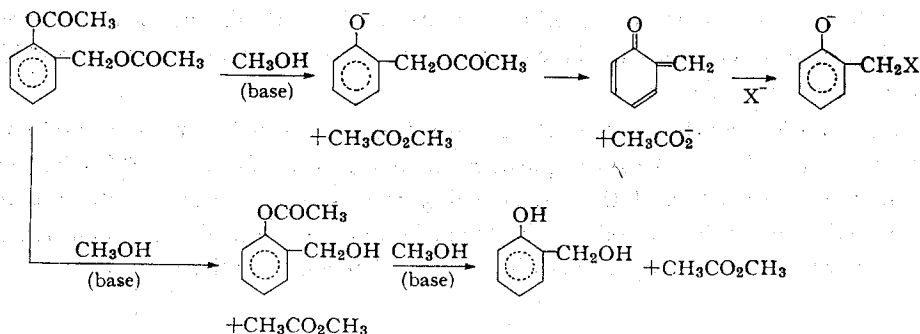
2-, and 4-Hydroxybenzyl compounds were obtained by refluxing the corresponding acetoxybenzyl acetates with the reagents, as shown in Table I. In all cases, the phenolic acetoxy group was transformed into phenol group during the reaction without special treatment.

Commonly an attempt to prepare alkyl, especially primary alkyl compounds by substitution of the corresponding alkyl esters with nucleophiles in protic solvents such as alcohol, primary or secondary amine is not successful unlike the case of the corresponding alkyl halides, because alkyl esters suffer acyl-oxygen cleavage by the attack of nucleophile in preference to alkyl-oxygen cleavage. For example, benzyl, 4-nitrobenzyl, 2-, and 4-methoxybenzyl acetate gave only the corresponding alcohols by acyl-oxygen cleavage when treated with a mixture of sodium azide and methanol. On the contrary, 2-, and 4-acetoxybenzyl acetate gave the hydroxybenzyl compounds by alkyl-oxygen cleavage as described above. A reaction path is illustrated by the following scheme for the reaction of 2-acetoxybenzyl acetate in methanol.

First, methanolysis of either phenolic acetyl ester group or benzyl acetyl ester group takes place. The result that 2-hydroxybenzyl compounds are obtained as the

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main product with a small amount of hydroxybenzyl alcohol shows predominant occurrence of the former reaction. Some basic substance seems to accelerate the reaction. Refluxing 2-acetoxybenzyl acetate in methanol without sodium acetate did not give 2-hydroxybenzyl methyl ether (**Io**). Though 2-hydroxybenzyl acetate afforded the same ether without sodium acetate, the reaction was very slow, while it was strongly accelerated by addition of sodium acetate. In some case, the nucleophile itself appears to play the role. The elimination of the acetoxy group from the phenoxide is thought to be facilitated by the formation of quinone methide except for the 3-isomer. The final product is formed by the addition of nucleophile to the quinone methide. Therefore, the formation of by-product due to the addition of the solvent is unavoidable. In fact, small amount of ethers (**Io**, **Ip**) was detected in the reaction mixtures of the azidations and the cyanations. These ethers, however, were easily removed in the isolation of the azides (**IVo**, **IVp**) which are new compounds, and the cyanides (**Vo**, **Vp**).

It is not unexpected that 2,2', and 4,4'-dihydroxydibenzyl disulfide (**VIIo**, **VIIp**) were obtained respectively instead of 2-, and 4-hydroxybenzyl mercaptan, since mercaptan is susceptible to air oxydation. Low yield of 4,4'-dihydroxydibenzyl disulfide is probably due to the formation of 4,4'-dihydroxybenzyl sulfide.

Table I. Reaction of Acetoxybenzyl Acetates

Product	Reagent	Time hr	Yield %
Io	$\text{CH}_3\text{COONa} + \text{CH}_3\text{OH}$	24	74
Ip	"	24	80
IIo	$\text{HN}(\text{C}_2\text{H}_5)_2$	3	76
IIp	"	1	80
IIIo	$\text{C}_6\text{H}_5\text{NH}_2 + \text{C}_6\text{H}_6$	24	75
IVo	$\text{NaN}_3 + \text{CH}_3\text{OH}$	2	68
IVp	"	2	75
Vo	$\text{KCN} + \text{CH}_3\text{OH}$	0.5	48
Vp	"	0.5	70
VIo	$\text{Na}_2\text{SO}_3 + \text{H}_2\text{O} + \text{CH}_3\text{OH}$	1	76
VIp	"	1	96
VIIo	$\text{NaSH} + \text{CH}_3\text{OH}$	1	74
VIIp	"	1	31
VIIIp	$\text{C}_6\text{H}_5\text{ONa} + (\text{C}_2\text{H}_5)_2\text{O}$	7	38

Only C-alkylation product was isolated in the reaction with sodium phenoxide, though two kinds of products, O-, and C-alkylation products were expected due to an ambident character of phenoxide ion.

2-, and 4-Hydroxybenzyl methyl ether (Io, Ip),^{6,7)} N-phenyl-2-hydroxybenzyl amine (IIIo),⁸⁾ sodium 2-, and 4-hydroxyphenylmethanesulphonate (VIo, VIp)^{2,4,9)} had been prepared by the reaction of the corresponding hydroxybenzyl alcohols with methanol, aniline and sodium sulfite or sodium bisulfite under more severe conditions, but no reaction occurred with hydroxybenzyl alcohol in our experimental conditions.

EXPERIMENTAL

2-Hydroxybenzyl Methyl Ether (Io): A mixture of 10.4 g. (0.050 mol.) of 2-acetoxybenzyl acetate, 4.1 g. (0.050 mol.) of anhydrous sodium acetate and 50 ml. of methanol was refluxed for 24 hr. After cooling, the solution was added to 150 ml. of water, neutralized with sodium bicarbonate and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was removed. Distillation of the residue gave 2-hydroxybenzyl methyl ether.^{6,10,11)} Yield 5.1 g. (74%), b.p. 80–82°/4 mm., n_D^{22} 1.5322. Found: C, 69.41; H, 7.60. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30.

4-Hydroxybenzyl Methyl Ether (Ip): A mixture of 10.4 g. (0.050 mol.) of 4-acetoxybenzyl acetate, 4.1 g. (0.050 mol.) of anhydrous sodium acetate and 50 ml. of methanol was treated in the same manner as described above. Yield 5.5 g. (80%), b.p. 115–117°/0.2 mm., m.p. 82–83°.^{6,7)} Found: C, 69.47; H, 7.48. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30.

N,N-Diethyl-2-Hydroxybenzyl Amine (IIo): A solution of 5.2 g. (0.025 mol.) of 2-acetoxybenzyl acetate in 25 ml. of diethylamine was refluxed for 3 hr. After removal of the excess diethylamine, the residue was added to 75 ml. of water, acidified with sodium bisulfite and extracted with ether. The aqueous layer was alkalized with saturated solution of sodium carbonate and extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was removed. Distillation of the residue gave N,N-diethyl-2-hydroxybenzyl amine.^{3,12,13)} Yield 3.4 g. (76%), b.p. 91–92°/0.4 mm., n_D^{32} 1.5100. Found: C, 73.20; H, 9.69; N, 7.71. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81.

N,N-Diethyl-4-Hydroxybenzyl Amine (IIp): A solution of 5.2 g. (0.025 mol.) of 4-acetoxybenzyl acetate in 25 ml. of diethylamine was refluxed for 1 hr. and treated in the same manner as described above except that the crude product was purified by recrystallization from benzene. Yield 3.6 g. (80%), m.p. 90.5–91.5°⁹⁾. Found: C, 74.43; H, 9.65; N, 7.66. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81.

N-Phenyl-2-Hydroxybenzyl Amine (IIIo): A solution of 1.3 g. (0.0063 mol.) of 2-acetoxybenzyl acetate and 1.7 g. (0.018 mol.) of aniline in 7 ml. of benzene was refluxed for 24 hr. After cooling, the solution was added to 30 ml. of 10% sodium hydroxide solution and the excess aniline and acetanilide were extracted with chloroform. The extract was dried over anhydrous sodium sulfate and the solvent was removed. The residue was recrystallized from carbon tetrachloride to give N-phenyl-2-hydroxybenzyl amine.^{8,14,15)} Yield 0.93 g. (75%), m.p. 113–114°. Found: C, 78.34; H, 6.63; N, 7.04,

Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03.

2-Hydroxybenzyl Azide (IVo): A mixture of 10.4 g. (0.050 mol.) of 2-acetoxybenzyl acetate, 4.9 g. (0.075 mol.) of sodium azide and 50 ml. of methanol was refluxed for 2 hr. After cooling, the mixture was added to 150 ml. of water and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate and the solvent was removed at room temperature. The residue was allowed to stand in a refrigerator for a few days until the most part solidified. The solid was filtered and recrystallized from carbon tetrachloride. Yield 5.1 g. (68%), m.p. 31–33.5°. Found: C, 56.41; H, 4.59; N, 28.09. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. It could not be distilled under the pressure of 10^{-3} mm.Hg. without decomposition.

4-Hydroxybenzyl Azide (IVp): A mixture of 10.4 g. (0.050 mol.) of 4-acetoxybenzyl acetate, 4.9 g. (0.075 mol.) of sodium azide and 50 ml. of methanol was treated in the same manner as described above except that the crude product was purified by column chromatography (silicic acid, solvent: chloroform). Yield 5.6 g. (75%), n_D^{28} 1.564. Found: C, 56.15; H, 4.76; N, 26.43. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. It could not be distilled under the pressure of 0.1 mm.Hg. without decomposition.

2-Hydroxybenzyl Cyanide (Vo): A mixture of 10.4 g. (0.050 mol.) of 2-acetoxybenzyl acetate, 4.9 g. (0.075 mol.) of potassium cyanide and 50 ml. of methanol was refluxed for 30 min. and treated in the same manner as described about 2-hydroxybenzyl azide. The crude product was triturated with a mixture of chloroform and carbon tetrachloride, filtered and recrystallized from chloroform. Yield 3.2 g. (48%), m.p. 120–122°¹⁶⁻¹⁸. Found: C, 71.70; H, 5.32; N, 10.20. Calcd. for C_8H_7NO : C, 72.16; H, 5.30; N, 10.52.

4-Hydroxybenzyl Cyanide (Vp): A mixture of 10.4 g. (0.050 mol.) of 4-acetoxybenzyl acetate, 4.9 g. (0.075 mol.) of potassium cyanide and 50 ml. of methanol was treated in the same manner as described above. Yield 4.7 g. (70%), m.p. 70–71.5°¹⁸⁻²⁰. Found: C, 72.23; H, 5.20; N, 10.62. Calcd. for C_8H_7NO : C, 72.16; H, 5.30; N, 10.52.

Sodium 2-Hydroxyphenylmethanesulphonate (VIo): A mixture of 1.3 g. (0.0063 mol.) of 2-acetoxybenzyl acetate, 1.2 g. (0.0095 mol.) of sodium sulfite, 3.5 ml. of methanol and 3.5 ml. of water was refluxed for 1 hr. The mixture was dried up and extracted with hot methanol. After removal of the solvent, the residue was recrystallized from aqueous ethanol. Yield 1.0 g. (76%)²¹⁻²³. Found: C, 39.82; H, 3.31. Calcd. for $C_7H_7SO_4Na$: C, 40.00; H, 3.36.

Sodium 4-Hydroxyphenylmethanesulphonate (VIp): A mixture of 1.3 g. (0.0063 mol.) of 4-acetoxybenzyl acetate, 1.2 g. (0.0095 mol.) of sodium sulfite, 3.5 ml. of methanol and 3.5 ml. of water was treated in the same manner as described above. Yield 1.26 g. (96%)^{24,25}. Found: C, 31.76; H, 5.05. Calcd. for $C_7H_7SO_4Na$: C, 40.00; H, 3.36.

2,2'-Dihydroxydibenzyl Disulfide (VIIo): A mixture of 1.3 g. (0.0063 mol.) of 2-acetoxybenzyl acetate, 0.75 g. (0.0094 mol.) of 70% sodium hydrogen sulfide and 7 ml. of methanol was refluxed for 1 hr. and treated in the same manner as described about 2-hydroxybenzyl azide. The crude product was recrystallized from carbon tetrachloride. Yield 0.64 g. (74%), m.p. 103–104°^{26,27}. Found: C, 60.76, H, 5.12. Calcd. for $C_{14}H_{14}O_2S_2$: C, 60.40; H, 5.12.

4,4'-Dihydroxydibenzyl Disulfide (VIIp): A mixture of 1.3 g. (0.0063 mol.)

of 4-acetoxybenzyl acetate, 0.75 g. (0.0094 mol.) of 70% sodium hydrogen sulfide and 7 ml. of methanol was treated in the same manner as described above. The crude product (0.87 g.) was recrystallized from aqueous ethanol. Yield 0.27 g. (31%), m.p. 174–177°. ²⁸ Found: C, 60.41; H, 5.08. Calcd. for $C_{14}H_{14}O_2S_2$: C, 60.40; H, 5.07.

4,4'-Dihydroxydiphenylmethane (VIIIp): A mixture of 1.3 g. (0.0063 mol.) of 4-acetoxybenzyl acetate, 2.2 g. (0.019 mol.) of sodium phenoxide and 25 ml. of ether was refluxed for 7 hr. After cooling, the mixture was added to 80 ml. of water, neutralized with sodium bisulfite and extracted with ether. The extract was dried over anhydrous sodium sulfate and the solvent was removed. The residue was triturated with a mixture of benzene and ethanol. The crude product was dissolved in a mixture of chloroform and ethanol, boiled with a small mount of alumina, filtered and cooled. 4,4'-Dihydroxydiphenylmethane was obtained as colorless prisms. Yield 0.48 g. (38%), m.p. 160–164°. ^{29,30} Found: C, 77.06; H, 6.04. Calcd. for $C_{13}H_{10}O_2$: C, 77.98; H, 6.04.

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